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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,674	02/14/2005	Hiroshi Nakayama	2005-0213A	8615

513 7590 04/11/2006

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EXAMINER	
JUNG, UNSU	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/524,674	NAKAYAMA, HIROSHI	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-33 and 48-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-47* is/are rejected.

7)☒ Claim(s) *36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/14/05 & 4/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendments to the specification in the reply filed on February 14, 2005 have been acknowledged and entered.

2. Claims 1-60 are pending.

Election/Restrictions

3. Applicant's election of Group III (claims 34-47) in the reply filed on February 14, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on April 26, 2005 has been considered by the examiner. However, there was a minor error in document "AP" as the beginning page number should be corrected to 8 as indicated on the IDS.

Drawings

5. The drawings are objected to because the Fig. 1A and Fig. 1B must be listed separately in the "Brief Description of the Drawings" of the specification (p15). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement

drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

6. The use of the trademarks CASCADE BLUE® (p25, line 17; p34, line 11; p35, lines 1, 6, 7, 10, 14, and 16; p36, lines 2, 6, 8, 11, 13, and 20; p37, line 25; p38, line 1, 5, 11, 16, 17, and 19; p39, lines 2, 13, and 14; p40, lines 9-10, 22, and 23-24; p41, line 20; p42, lines 5, 7-8, and 10; p43, lines 7, 12, 13, and 15; p44, lines 8-9 and 10; p45, lines 15, 18, 19-20, and 24; p46, lines 2 and 7), SEPHADEX™ (p35, line 9), and BACLIGHT™ (p37, line 22; p41, line 8; and p46, line 4) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

7. Claim 36 is objected to because of the following informalities: a comma is needed following the word "agents" in line 3. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 34-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. In claim 34, the phrase "having a positive or negative charge in the sample" in line 5 is vague and indefinite. It is not clear whether or not the phrase "having a positive or negative charge in the sample" is referring to "charge control agent" in lines 3-4. For the purpose of examination, the phrase has been interpreted as being referring to the "charge control agent" in lines 3-4.

11. In claim 34, the phrase "resulting from the mixing" is vague and indefinite. It is not clear whether or not the phrase "resulting from the mixing" is referring to the binding of the charge control agent to the target particle. For the purpose of examination, the phrase has been interpreted as "separating or quantitatively determining the target particle provided with the charge control agent bound thereto, based on a surface charge modified by the binding of the charge control agent resulting from the mixing, by applying a voltage or current to the sample.

12. In claims 35 and 36, the term "particles" in line 2 is vague and indefinite. It is not clear whether or not the term "particles" is referring to the "target particle" in claim 34.

13. In claim 36, the term "charge control agents" in line 3 is vague and indefinite. It is not clear whether or not the term "charge control agents" is referring to the "charge control agent" in claim 34.

14. In claims 40, 43 and 45, the phrase "a functional equivalent thereof" is vague and indefinite. It is not clear what is being defined by the phrase "a functional equivalent thereof" as the specification does not define the phrase with respect to aptamer or ligand.

15. In claims 42 and 43, the phrase "the marker bound thereto" is vague and indefinite. It is not clear whether the phrase "the marker bound thereto" means that the

marker is bound to the charge control agent or target particle. For the purpose of examination, the phrase has been interpreted as being the marker is bound to the charge control agent.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 34-39, 41-44, and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Kopf-Sill et al. (U.S. Patent No. 6,524,790, Filed June 9, 1997).

Kopf-Sill et al. teaches a method of separating or quantitatively determining a target particle (analyte) in a sample, the method comprising the steps of:

- mixing a sample containing the target particle and a charge control agent such as an antibody or a nucleic acid, which specifically binds to the target particle (column 30, lines 31-52) and having a positive or negative charge in the sample (column 2, lines 36-50), and binding the charge control agent to the target particle (column 30, lines 31-52); and

- separating or quantitatively determining the target particle provided with the charge control agent bound thereto (column 1, lines 20-24), based on a surface charge modified by the binding of the charge control agent resulting from the mixing, by applying a voltage or current to the sample (column 30, lines 31-52).

With respect to claims 35 and 36, Kopf-Sill et al. teaches the method of claim 34, wherein the mixing step is separately performed for a plurality of types of particles with respective charge control agents, which are different from each other (column 26, lines 8-23).

With respect to claim 37, Kopf-Sill et al. teaches the method of claim 34, wherein the target particle is selected from a group consisting of a bacterium, a virus, and a fungus (column 35, lines 13-23).

With respect to claim 38, Kopf-Sill et al. teaches the method of claim 37, wherein the charge control agent is bound to a biological functional substance selected from a group consisting of an organic polymer and a protein (column 31, lines 2-35).

With respect to claim 39, Kopf-Sill et al. teaches the method of claim 38, wherein the charge control agent comprises a protein and a peptide (column 6, lines 44-55).

With respect to claims 41 and 46, Kopf-Sill et al. teaches the charge control agent further comprising a marker having a positive or negative charge in solution such as gold colloid or latex (column 28, lines 4-6).

With respect to claim 42, Kopf-Sill et al. teaches the method of claim 41, wherein the charge control agent is a complex composed of an antibody, which is capable of

specifically binding to the biological functional substance and the marker bound to the antibody (column 7, lines 1-4).

With respect to claim 43 and 44, Kopf-Sill et al. teaches the method of claim 41, wherein the charge control agent is a complex composed of a ligand for a receptor present on the surface of the target particle and the marker bound to the ligand. Furthermore, Kopf-Sill et al. teaches a method, wherein a cytokine receptor is being assayed (column 31, lines 2-8), which would necessarily need a cytokine as a ligand. Therefore, Kopf-Sill et al. anticipates the limitations of the ligand being a cytokine in claim 44.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. Claims 40 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf-Sill et al. (U.S. Patent No. 6,524,790, Filed June 9, 1997) in view of Janjic et al. (U.S. Patent No. 6,329,145, Dec. 11, 2001).

Kopf-Sill et al. teaches a method of separating or quantitatively determining a target particle in a sample as discussed above. Kopf-Sill et al. teaches a variety of binding agents (charge control agent) such as antibodies, proteins, receptor ligands, and nucleic acids (column 30, lines 31-52) labeled directly with fluorescent and colorimetric labels (column 27, line 64-column 8, line 37). However, Kopf-Sill et al. fails to teach a method, wherein the charge control agent is an aptamer bound with a maker.

Janjic et al. teaches that aptamers (also termed nucleic acid ligands) are structurally unique nucleic acids capable of binding other molecules such as proteins, peptides, carbohydrates, and other organic molecules with high affinity and specificity (column 1, lines 33-45). Specifically, aptamers bind to protein targets including growth factors, enzymes, receptors and structural proteins in a highly specific manner (column 1, lines 45-49). High affinity binding of aptamers for protein targets is typically encoded in sequences of 20-40 nucleotides and the efficient encoding of high affinity binding allows aptamers to be synthesized entirely chemically, e.g. by the solid phase synthesis (column 5, lines 18-22). Aside from the advantage of being able to control batch-to-batch variability and lower reagent cost, chemical synthesis facilitates the incorporation of various non-nucleic acid functionalities into aptamers in a manner that does not disrupt their exquisite binding properties (column 5, lines 22-27). Therefore, aptamers can be labeled in a variety of other ways such as light-absorbing, fluorescent or

chemiluminescent moieties that may be more suitable for some high throughput screening applications (column 5, lines 27-31).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use aptamer labeled with a marker such as fluorescent or chemiluminescent moieties as taught by Janjic et al. in the method to detect biological substances such as receptors and other protein molecules on cell surface as taught by Kopf-Sill et al. because aptamers provide high affinity and specific binding of protein targets with an advantage of having lower reagent cost of synthesis and controlled batch-to-batch variability. In addition, aptamers have further advantage of including the labeling step during the synthesis in a manner that does not disrupt their binding properties and would therefore not require additional step of labeling following the synthesis.

21. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf-Sill et al. (U.S. Patent No. 6,524,790, Filed June 9, 1997) in view of Molnar et al. (*Biochemica et Biophysica Acta*, 1991, Vol. 1068, pp27-40) and Whitaker et al. (*Analytical Biochemistry*, 1991, Vol. 198, pp119-130).

Kopf-Sill et al. teaches a method of separating or quantitatively determining a target particle in a sample as discussed above. Kopf-Sill et al. teaches a variety of binding agents (charge control agent) such as antibodies, proteins, receptor ligands, and nucleic acids (column 30, lines 31-52) labeled directly with fluorescent and colorimetric labels (column 27, line 64-column 8, line 37). However, Kopf-Sill et al. fails

to teach a method, wherein the fluorescent label is an azido derivative of Cascade blue, aminoehtyl14-azidebenzamide trisodium salt (ACB).

Molnar et al. teaches an azido-derivatives of Cascade Blue, such as ACB (p30, Fig. 1). However, Molnar et al. fails to teach that ACB can be used to conjugate or label a charge control agent.

Whitaker et al. teaches that blue fluorescent dyes such as Cascade Blue derivatives are suitable for a variety of biological, immunological and histochemical applications (p120, right column, lines 26-28). Specifically, Cascade Blue derivatives can be conjugated with antibodies (pp123-124, *Indirect Immunofluorescence Staining*) in a detection assay with advantages of being readily soluble in aqueous preparations, insensitive to pH, minimally quenched on conjugation with macroscopic molecules and show low overlap with the emission spectra of commonly used green or yellow fluorescent dyes such as fluorescein and Lucifer Yellow (p120, right column, lines 4-15).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a blue fluorescent dyes such as ACB of Molnar et al. to label a charge control agent such as antibodies as taught by Whitaker et al. in the method of Kopf-Sill et al. in order to detect a target particle in a immunological binding assays as Cascade Blue derivatives has several advantages, which include being readily soluble in aqueous preparations, insensitive to pH, minimally quenched on conjugation with macroscopic molecules and show low overlap with the emission spectra of commonly used green or yellow fluorescent dyes. The properties of the dye having high solubility of the dye in aqueous solution would optimize the utility of the dye for modification of

proteins and insensitive pH would be enable measured signal to be proportional to the absolute quantity of the dye present and not the pH of the solution during an assay.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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